Journal of the American College of Cardiology Vol. 61, No. 7, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.11.034

EDITORIAL COMMENT

Success in Recruitment to Randomized Clinic Trials

Keep it Simple and Close to Home . . . or Is There More to It?*

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Randomized clinical trials (RCTs) are accepted as the best way to evaluate the effectiveness of treatments, but have been consistently plagued by difficulties in recruiting enough participants. Most RCTs take longer than expected to recruit the planned sample size, or miss their enrollment targets completely. Clearly, we need to understand how to recruit participants in these important studies.

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In this issue of the *Journal*, Martin et al. (1) report an interesting analysis of factors that influenced whether patients approached for participation in randomized trials agreed to be enrolled and randomized. The investigators analyzed data from screening logs of 15 cardiovascular randomized trials conducted at Duke University Medical Center, and identified the trial-specific and patient-specific factors that significantly affected study participation. Based on a careful multivariable analysis, the authors conclude several trial-specific factors had a significant, negative effect on participation, namely, longer trial duration and more protocol-driven tests. They also found that the patient-specific factors most associated with nonparticipation were older age and female. Interestingly, a patient's level of education, income, and race did not seem to have an effect upon willingness to participate in an RCT.

Professor Peter Sleight (2) once noted that "Simple trials answer the questions rapidly and effectively. The mechanics of the trial do not hinder patient entry by participating doctors and nurses." His comments are consistent with the findings of Martin et al. (1), and remind investigators planning RCTs to "keep it simple." That is not easy to do, as the natural tendency of those engaged in clinical trials is to explore additional questions by obtaining more data, which makes the trial more difficult to perform, and may tax trial participants to the breaking point. My own experience in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial, which included close follow-up, with visits every 3 months to the research site, was that the protocol was too demanding for many working patients, as well as for older patients with limited mobility. Participants frequently commented on the challenge of arranging transportation to visits or the need to miss work. The suggestion by Martin et al. (1) to consider innovative follow-up strategies, such as collecting follow-up data on the Internet, might make trial participation more attractive to patients. We should not forget that the patient's willingness to be a research subject is enhanced when investigators make it as easy as possible to participate, and omit needless tests, visits, and questions.

Although it was not an independent predictor, patients with prior contact with the study center seemed more likely to agree to participate in RCTs, perhaps reflecting the importance of familiarity with the study center, and the support of their personal physician for the recruitment effort. Evidence abounds of successful recruiting for trials by individual physicians who practice outside an academic health center. That suggests that recruitment might be more successful if the investigators "keep it close to home."

Improved recruitment of women and the elderly in RCTs has been identified as a priority, because they may have distinct clinical characteristics, modes of presentation, and outcomes. The Duke experience confirms the challenge in recruiting more women and elderly patients into RCTs. We need to do better, and we need to identify barriers to their participation. The lack of an effect of race on patient willingness to participate in RCTs is a welcome surprise, as many African Americans lack trust in clinical trials after the sorry legacy of Tuskegee and other experiments. The strategies used at Duke to enhance minority recruitment would be of interest to all.

While recruitment failures and delays in clinical trials have led to workshops at the Institute of Medicine and National Heart, Lung, and Blood Institute (3,4) to address shortfalls, there are also examples of exceptional success in recruitment to clinical trials. The TIMI (Thrombolysis In Myocardial Infarction) study group and Duke Clinical Research Institute regularly recruit large numbers of patients in a timely manner. We need to understand the basis for their success. Yet even with their overall success, recruitment in North America has been declining, and many trials now depend on foreign sites to enroll sufficient numbers of patients. For example, only 1,814 of the 18,000 patients recruited in the PLATO (Platelet Inhibition and Patient Outcomes) trial were from North America.

Why is it necessary to recruit so many patients in other countries? In my judgment, a key issue in the United States

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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is the doctor-patient relationship. The patient comes to the doctor because of a complaint, not to participate in a trial. The process of random assignment to a treatment or strategy may lead to confusion and uncertainty in the mind of the patient. Do we understand the patient's true perceptions of decisions made by random assignment? While many argue it is in the patient's best interest to participate in a randomized trial, some remain suspicious, exemplified by a recent book entitled "What the Doctor Didn't Say: The Hidden Truth About Medical Research" (5). Patients may be unwilling to accept randomization if they might not receive the treatment they regard as the best, or drop out if they do not receive the treatment they prefer, particularly when it is available outside the trial. Although most trials allow for "crossover" to the alternate therapy if deemed clinically necessary, stories in the press (6) about an episode in which a patient in a cancer trial was not allowed to cross over may lead some patients to refuse to participate.

Drazen (7), in an excellent editorial on transparency in clinical trials, states, "We can make progress in medicine only if people are willing to put themselves at risk to test new diagnostic and therapeutic approaches." In my opinion, this is the fundamental challenge in recruitment; our approach must always be guided by the ethical concerns of Katz (8) regarding the "intertwining of medical science and medical practice." From the point of view of the physician involved in a clinical trial, with equipoise, one should be able to look the patient in the eye and confess uncertainty about the best option for treatment or diagnostic strategy; and recommend trial participation. But what does the patient actually think? Will understanding the patient's concept of the research enhance recruitment? One hopes that Martin et al. (1) will pursue these challenging questions in future studies.

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Key Words: trial enrollment ■ trial participation ■ trial representation.